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AMERICAN SOCIETY OF CLINICAL ONCOLOGY

April 4, 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Regarding: Draft Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims [Docket No. 2006D-0044]

Dear Sir or Madam:

With more than 23,000 members worldwide, the American Society of Clinical Oncology (ASCO) is the leading medical society for physicians involved in cancer treatment and research. ASCO members are involved in cancer clinical trials supported by both federal funding sources and the pharmaceutical industry and thus have a strong interest in the subject of this draft Guidance.

ASCO commends the Food and Drug Administration (FDA) for taking the next step on the issue of patient-reported outcomes (PROs), consistent with recommendations in our earlier comments on this topic. Hopefully, this guidance will result in broader and more consistent application of such measures in cancer clinical trials. Although PROs may not be adequate to support approval decisions, such information may be valuable to clinicians and patients if it were included in the labeling. As stated in our previous comments, more information about the full range of symptoms and outcomes confronting survivors would be useful, not only in better understanding the effects of investigational drugs, but ultimately in determining the course of therapy.

ASCO is devoting significant resources to improving quality cancer care, an integral part of which is better measurement of patient-reported outcomes. Though validated tools currently exist to assess many domains that are of importance in clinical research, there is a need for methodologic research to improve PRO instruments that assess these domains and other domains of a patient's condition, as well a need for additional methodologic research about the interpretation of outcome scores and the statistical analysis of data that includes missing data points.

In general, the guidance is comprehensive, well written, and addresses the complexity of PRO measures. Since it covers many issues in depth, an executive summary highlighting key points would be helpful for both sponsors and practitioners.

Realizing the importance of PROs to the physician and patient communities, ASCO offers the following specific comments for further clarification or development in the guidance document:

Protocol Design

One strength of the guidance is its emphasis in many places on the need to plan for the incorporation of PRO instruments as an integral part of study design. ASCO agrees that this is extremely important and commends the FDA for underscoring this point. Because it is so critical that PRO instruments be incorporated during the protocol design phase, the guidance might be better served by placing the section on Study Design at the beginning of the document to provide additional emphasis.

ASCO feels the following points are also important to consider when designing a clinical trial with PRO instruments: the outcomes being measured; respondent burden; interpretation of the data; and how the final data are presented to the regulatory and medical communities, specifically in a way that is complete and comprehensible. We also recommend that specific hypotheses be stated in the protocol with respect to the magnitude of change expected in the PRO measurement as a result of the intervention and that the study have an adequate sample size to detect this change.

Missing Data

ASCO appreciates the FDA's recommendations regarding missing data and, recognizing that there is still progress to be made regarding assumptions about missing data. ASCO agrees that protocols should specify methods for both minimizing and analyzing missing data. In addition, every effort should be made to minimize missing data by considering factors such as the patient population being studied, the outcomes being measured, and at what point in the course of the study the observations are being analyzed compared to baseline. It is clearly important that procedures for defining and interpreting missing data be specified when the protocol is designed.

Performance of Daily Activities

We are not aware of evidence that asking respondents about their capacity to perform tasks is less desirable than asking about actual performance. The guidance seems too restrictive on this point. ASCO recommends that protocols state whether measures of patient-reported capacity or patient-reported performance (or both) will be used and why the chosen instruments are appropriate for that protocol. Unless investigators are permitted to select their measures (some of which measure both capacity and performance), this "not recommended" guidance may hold PROs to a different standard than clinical endpoints.

PRO Instruments in Unblinded Studies

ASCO recognizes FDA's concern regarding the potential bias of PRO instruments used in studies where the treatment is known to the patient and/or the investigator and agrees that the most unbiased data result from blinded, controlled studies. In the field of oncology, however, blinding is not always possible due to the toxicity associated with a given regimen. ASCO is concerned about FDA's statement that open-label trials are "rarely credible" and recommends that lines 717-718 be amended to read: "Because responses to PRO measures are subjective, representing a patient's impression, ***data from*** open-label studies, where patients and investigators are aware of assigned therapy, ***must be interpreted thoughtfully and carefully***." To facilitate the use of instruments to capture important patient health information and ensure the value of the data collected, PRO instruments should be designed to minimize bias in the unblinded setting by analyzing the internal consistency of the data set. If all domains and outcomes being measured are consistent, the results will be more credible. As more targeted therapies with less toxic side effect profiles are used in oncology, blinded studies are likely to become more feasible.

Minimum Important Difference (MID)

ASCO agrees with FDA's guidance on interpretation of study results, especially concerning the implications for study design when relating MID to clinically meaningful differences. When a study is designed, there is a need to choose a PRO instrument that appropriately measures the outcome of interest and determines that this outcome has a clinical interpretation. The study should be sized so that there is adequate power to detect clinically meaningfully differences or changes in the PRO instrument that is measuring the domain(s) of interest.

Conceptual Framework

Although there are multiple competing frameworks that have been proposed, ASCO recommends the FDA consider the following definition by Gotay et al[1]:

"For HRQOL (and also patient perceptions of care and needs assessment), conceptual models are required that include a theory that specifies which domains are to be included in the HRQOL measurement model, the relationships among the various domains, the relative importance of the domains, and a causal pathway that clearly distinguishes causal from indicator variables . . . and that specifies the relationships between them.[1]"

Toxicity Data

The Common Toxicity Criteria (CTC) are currently used to assess both subjective and objective toxicity data. Although the CTC and PRO measures are different tools used for distinct purposes, ASCO believes it would be desirable to perform additional research regarding congruence between the CTC and PROs to provide a better understanding of the similarities and differences in outcomes based on the data collected.

Conclusion

ASCO recognizes the effort FDA has put into creating the PRO Draft Guidance. By addressing this issue, the FDA will facilitate the use of PRO instruments as a tool to measure effective endpoints in clinical trials, in addition to survival. The guidance will also enable sponsors to develop and use study results to support claims in approved product labeling. ASCO appreciates the opportunity to participate in the agency's policy development and hopes the exchange of views will serve to improve the medical product development and evaluation process.

Sincerely,

Joseph S. Bailes, MD
Interim Executive Vice President and CEO

[1] Gotay CC, Lipscomb J, Snyder CF: Reflections on findings of the cancer outcomes measurement working group: Moving to the next phase. J Natl Cancer Inst 97: 1568-1574, 2005